ROLE OF DIAZEPAM AND PIRACETAM IN THE MANAGEMENT OF BREATH-HOLDING SPELLS IN CHILDREN

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CERTIFICATE

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DECLARATION

I declare that this dissertation entitled **"ROLE OF DIAZEPAM AND PIRACETAM IN THE MANAGEMENT OF BREATH-HOLDING SPELLS IN CHILDREN"** has been conducted by me at the Institute of Child Health and Hospital for Children, Egmore, Chennai – 600 008, under the guidance and supervision of my unit Chief **Prof.Dr.R.Kandasamy, M.D., D.C.H., Prof.Dr.N.Thilothammal, M.D., DM (Neurology)** and **Prof.Dr.V.Jayanthini, M.D., D.P.M., F.I.P.S.,** It is submitted in part fulfillment of the award of the degree of **M.D. (Paediatrics)** for the March-2009 examination to be held under **The Tamilnadu Dr.M.G.R.Medical University, Chennai**. This has not been submitted previously by me for the award of any degree or diploma from any other University.

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CONTENTS

INTRODUCTION

Breath holding spells are dramatic, involuntary episodes that occur in otherwise healthy children. These episodes are often frightening to parents until the situation is defused by explanation and reassurance. The attacks are self limited and usually outgrown by school age.

BHS are a well recognised common problem affecting about 27% of healthy children[1]. Childhood breath holding conjures up an image of a stubborn toddler wilfully holding his breath until he gets what he wants. The reality is quite different however.

Two main types of BHS were described by Lombroso & Lerman[2] – the cyanotic and pallid forms, according to the skin colour changes occurring during the episodes. Pallid BHS result from exuberant vagally mediated cardiac inhibition. Cyanotic BHS are of more complex pathogenesis, involving an interplay among hyperventilation, valsalva maneuver, expiratory apnea and intrinsic pulmonary mechanisms. The history is the mainstay of diagnosis; videotape documentation may be possible.[3]

The age of onset is generally below 18 months[4, 5]. Breath holding is not infrequently observed in the early weeks of life and has been described in the early newborn period also[5,6]. Usually cyanotic BHS begin between a child's neonatal period and 18 m of age. For pallid BHS, the age of onset is 12 m to 24m. By 24 m, almost all children who experience breath holding will have had their first episode.

Boys and girls appear equally susceptible[5]. Attacks are usually precipitated by

situations associated with anger, frustration or agitation. Pain and fear may also be the inciting factors.

The frequency of attacks varies greatly, ranging from very occasional attacks to several times a day. The greatest frequency of events tends to be in the second year of life. More commonly, patients have several episodes a week, and overall occurrences ranges from daily to monthly. By the time patients are 4 yrs old, about half of BHS cases have spontaneously resolved; by age 6 about 90% have done so; and by 7 or 8 yrs virtually all have resolved[2,7].

Most of the children are neurologically and intellectually normal, but associated behavioural problems are common. However these behaviour disturbances are in no way characteristic.[5]

CYANOTIC ATTACKS

This is the most common type of BHS. Anger, frustration and painful stimuli such as a fall are common triggers. After such a stimulus, the child cries, stops breathing in expiration, and becomes cyanosed, limp and unconscious. In the shorter attacks he/ she gains consciousness within a few minutes and may resume crying. If apnea lasts longer, the limp phase is followed by an ophisthotonic phase, sometimes with clonic movements of the limbs and sometimes incontinence of urine or faeces. This clonic phase may be followed by another limp phase before consciousness is regained.[2]

PALLID ATTACKS

These are termed 'reflex anoxic seizures' by Stephenson (1978)[7]. The pallid attack comes on a few seconds after a sudden unexpected and mildly unpleasant stimulus. This is often a moderate or mild knock on the back of the head, the first experience of a bath or a new taste which may surprise and upset the child. He gasps and becomes apneic and unresponsive, usually without significant crying; he is limp, deathly pale and seems to his parents to be dead, but usually returns fairly rapidly to normal, although he may sleep afterwards. However it is common for ophisthotonus, a few clonic movements and upturning of eyes to occur.

Although it is a much less likely scenario, BHS may be secondary to CNS malformations, such as Arnold- Chiari malformation[7]. Spells may be associated with developmental disorders such as Rett syndrome or with Riley- Day syndrome, a familial dysautonomia.[7] Sporadic reports have linked BHS with underlying hematologic abnormalities including transient erythroblastopenia of childhood and iron deficiency states[9,10]. In the latter case, treatment with iron supplements was found to significantly reduce the number of spells[10].

AETIOPATHOGENESIS

The aetiology of BHS is not yet clear. Some workers have related its origin to the child's temperament[11], parental attitudes[11], iron deficiency[2,12], or constitutional hypervagotonia[1]. Recently DiMario F.J. Jr has shown that autonomic nervous system

dysfunction is the basic underlying pathology in children with BHS[13,14]. The study by Anil B.G. et al., in India showed that subtle underlying autonomic nervous system dysregulation was present in children with BHS[15].

MECHANISMS POSTULATED

Emotional factors are certainly involved. The attacks are most frequent during normal developmental phase of negativism. Many of the affected children are described by their parents as being demanding and rather stubborn children[4].

Hereditary and familial factors are also important. Previous observations have noted that perhaps 20–30 % of children with benign BHS have family members who are affected during their childhood[7,16]. In addition, data from detailed analysis suggest an autosomal dominant mode of inheritance in some cases of severe BHS[16]. Vulliamy (1956) suggested that the basic mechanism was an acute reduction in cerebral blood flow produced by a sharp rise in intrathoracic pressure or valsalva like maneuver caused by breath holding in expiratory phase. The initial hyperventilation caused hypocapnia and this caused cerebral vasoconstriction. Then, when breath was suddenly held in expiration, the increased intrathoracic pressure causes a decrease in the effective perfusion pressure in cerebral arteries by increasing the jugular venous pressure and/ or decreasing carotid artery pressure[4].

Lombroso & Lerman[2] proposed that the two types of BHS are caused by two different mechanisms. In the cyanotic BHS, they agreed with the mechanism suggested

by Vulliamy. In the pallid BHS, they thought that there was sudden circulatory failure secondary to cardiac asystole. In both types of BHS, acute cerebral anoxia was the end result and was responsible for the loss of consciousness. They also demonstrated marked generalised slowing of activity in the EEG during the early hypoxic stage of the attack. It was followed by flattening of the record if the attack was prolonged and cerebral anoxia supervened. They suggested that electrical silence in the EEG was probably due to cessation of cortical neuronal activity and that the stiffening, ophisthotonus and the tonic seizures occasionally seen in the prolonged attacks were due to the release of brainstem structures from the control of corticoreticular inhibitory fibres.

Recently DiMario by his studies has shown that there is generalised autonomic dysfunction in children with BHS. This dysregulation may contribute to the pathophysiology of severe BHS in these children[13,14].

Kohyama J et al., studied REM sleep in breath holders[17]. He performed one night polysomnography on seven subjects suffering from BHS, including one whose death was suggested to be the consequence of a breath holding spell. The average number of both REMs and bursts of REMs in REM sleep in the breath holders were significantly lower than those in age-matched controls. Since the rapid eye activity is generated in the brainstem, the authors hypothesised that a functional brainstem disturbance is involved in the occurrence of BHS.

Kahn et al., investigated the possibility that infants with breath holding spells

have breathing disorders during sleep[18]. The infants were studied during a one-night monitoring session and the 142 sleep recordings were analysed. The authors concluded that the obstructed breathing during both wakefulness and sleep could be related to a common immature breathing control.

ROLE OF IRON DEFICIENCY ANAEMIA IN BHS

Many authors[9,10,19,20] have reported an association of iron deficiency anaemia with breath holding spells and improvement with iron therapy. The age of onset and presentation of spells occur during the period of maximum iron deficiency. As the child starts consuming diet with better iron content, the illness starts waning[19].

It is not known how iron deficiency leads to BHS. Iron deficiency may lead to adverse effects on oxygen uptake in the lungs and reduces availability of oxygen to tissues, including the central nervous system. Iron also plays an important role in catecholamine metabolism and the functioning of neurotransmitters and enzymes in the CNS. The correction of spells during treatment with iron may be related to the functional restoration of these neurotransmitters[20].

Orii et al., evaluated the autonomic nervous system of patients with BHS after treatment with iron. They found that iron supplementation improves the dysregulation of the autonomic nervous system reflexes[21].

PROPOSED MECHANISMS FOR THE OCCURRENCE OF BHS

1. Social and emotional factors[4,11]
2. Hereditary and familial factors[7,11,16]
3. Familial hypervagotonia[1]
4. Autonomic nervous system dysfunction[13,14]
5. Functional brainstem disturbances[17]
6. Iron deficiency[9,10,19,20]

PALLID BREATH HOLDING SPELLS

Unexpected/ unpleasant stimulus

↓

Vagally mediated asystole

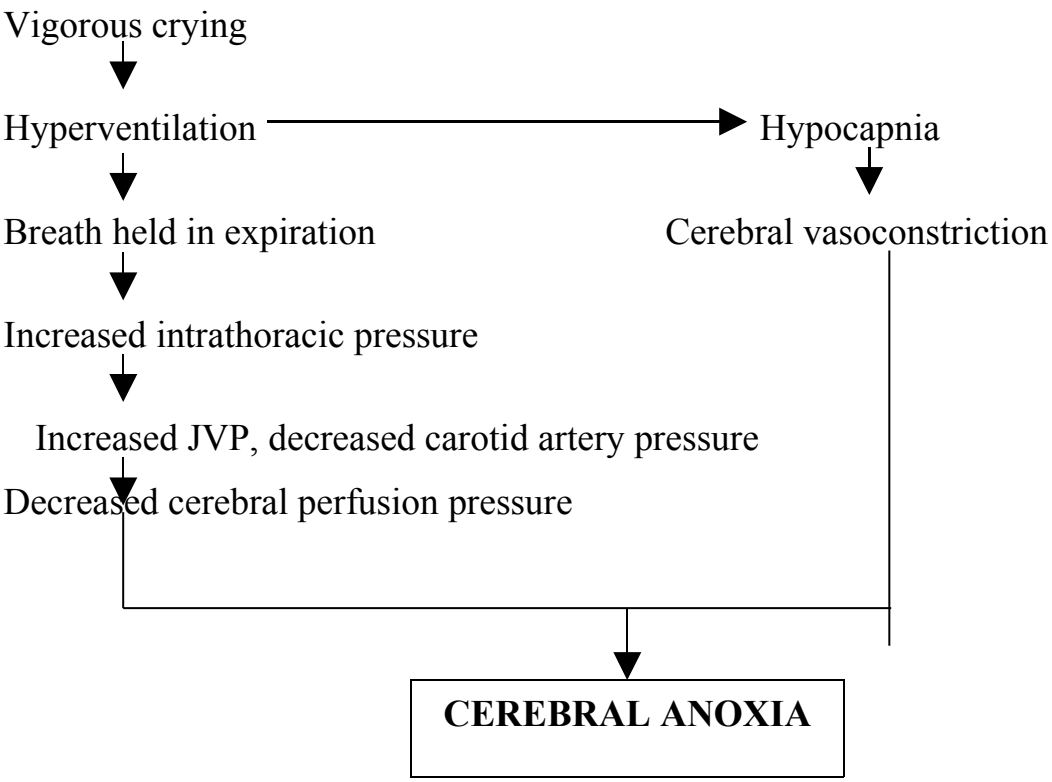
↓

Sudden circulatory failure

↓

Cerebral anoxia

CYANOTIC BREATH HOLDING SPELLS



MANAGEMENT

COUNSELLING AND BEHAVIOR MODIFICATION

It is important to assure the parents that although BHS are frightening to observe, they are benign and children outgrow them. Also, the parents should be told that evidence suggests no serious long term effects of benign BHS in otherwise healthy children; these patients don't have increased risk of epilepsy or other neurologic problems. The only significant finding on subsequent follow up of children with BHS was a mildly increased incidence of syncope later in life, especially in childhood or adolescence[2]. Later syncope is rare in children with cyanotic BHS, whereas it occurs in 17% of children with pallid BHS[7]. Adequate education of caregivers about BHS, alleviation of their anxiety about these episodes is essential. Because of fear parents may try to prevent every conflict or minor mishap in a child's life. Such efforts are neither practical nor possible and may lead parents to overindulge their child or to forego appropriate discipline to pacify him/her. Behaviour problems may ensue.

Nevertheless, when a child with BHS becomes upset or cries, reasonable efforts to calm the child or distract his attention should be made. If an episode occurs despite these measures, observation of the child and prevention of injury are generally all that is required. If a child loses consciousness, he should be placed in left lateral position to avoid injury and possible aspiration. As he recovers he should be left to himself. The parents should display an attitude of unconcern to prevent the child from gaining satisfaction by his performance and using the attacks to dominate the family.

IRON THERAPY

Treatment of concomitant iron deficiency anaemia with ferrous sulphate (6mg/kg/ day) has been reported to decrease the frequency of spells[10,20]. Iron has also been found to reduce the autonomic nervous system dysfunction in children with BHS[21].

ATROPINE

In severe cases with associated bradypnea or asystole or in patients with severe pallid BHS with multiple daily episodes, a 0.1 mg of oral atropine three times daily has been found to be effective in preventing pallid BHS.

ANTICONVULSANTS

Various drugs such as diazepam, sodium valproate, carbamazepine and phenobarbitone have been used for the control of anoxic seizures in breath holding spells[3,22,28]. These drugs may be useful in control of seizures but there is no definitive evidence about their role in reduction of frequency or severity of breath holding spells. Diazepam is a benzodiazepine, with a high therapeutic index and is safe in children. It is a selective anxiolytic, hypnotic, muscle relaxant and anticonvulsant. It acts on the limbic system, and also reduces the hypersensitivity of the autonomic nervous system. It acts on the GABA-A chloride channel receptor complex and facilitates the action of GABA[29]. Regular use of low dose diazepam for reduction of the frequency or severity of spells has not been studied before. Its effect on the temperament and aggressive behaviour of difficult children has led to its off-label use for the treatment of breath holding spells.

NEWER MODALITIES OF THERAPY

PIRACETAM

Piracetam is a newer anti epileptic drug. It enhances learning and memory. It acts on the cholinergic system in the cortex and hippocampus, and has a protective effect against cerebral hypoxia. It possesses very few side effects and is safe in children. It is used in treatment of refractory seizures, in cranio-cerebral injuries and strokes. Its efficacy in treatment of aphasia and other behavioural abnormalities (cognitive disorders) has also been studied.

MECHANISM

Piracetam participates in the activity of the majority of neurotransmitters, increases glucose and oxygen consumption in the ischemic nervous tissue and increases blood flow through cerebral terminal vessels. In cranio-cerebral injuries, it is found to improve cerebral blood flow. Piracetam is also found to increase the inhibitory hyperpolarising process in a manner similar to that of GABA.[23,30]

PACEMAKER IMPLANTATION

Kelly A. M. et al., showed usefulness of pacemakers in the treatment of severe breath holding spells associated with significant bradycardia[25]. They treated ten pediatric patients with apparent breath holding spells with bradycardia with a permanent ventricular demand pacemaker at the Mayo Clinic USA between 1985 and 1995. Permanent ventricular demand pacemakers were implanted at 10 months to 5 years of age. At follow up of 38 to 170 months (median 65.5), 5 patients had complete resolution

of spells, 2 had only mild colour change without loss of consciousness or seizure activity, and 3 continued to have minor brief spells. The study concluded that pacemaker implantation for children with pallid breath holding spells associated with severe bradycardia is safe, efficacious and warranted.

In another prospective study, Villain E. et al., paced 11 children with severe breath holding spells[26]. The results were spectacular with disappearance of spells and restoration of normal activities. 2 patients were lost to follow up and only 5 were still vagotonic. The study concluded that pacemaker implantation is very effective in suppressing symptoms in severely affected children.

REVIEW OF LITERATURE

Bhatia M. S. et al., (1990) evaluated 50 children with the diagnosis of BHS so as to find out the socio-demographic profile, role of parental attitudes and iron deficiency[23]. Of 50 preschool children having BHS, 80 % were less than 18 months of age (mean 16 months). More children came from lower social class (70%) and a nuclear family (65%). Boys to girls ratio was 3:1. 48 (96%) children had cyanotic type of BHS and 2 (4%) had pallid type of BHS. Tonic and clonic spasms were present in 84% children. Ninety percent children had spells when angry or frustrated, followed by 10% associated with falls. Majority of the children had frequency of spells as 1-3 attacks per week with a minimum of one per month and maximum of 12 per day.

The study did not find any significant association between the parental attitudes (measured on Attitude Screening Questionnaires) and BHS. No significant differences could be found as far as behaviour related to feeding, toilet and sleep were concerned. But the children with BHS had problems in socialisation and more children reacted strongly to the environment. They were more demanding and irritable in nature, difficult to soothe and could not be left alone in a new situation. Associated behavioal problems like pica (16%), thumb sucking (14%), nail biting (10%), head banging (8%), sleep disturbances, hyperkinesis (8%), tics (6%), enuresis (4%) and stammering (6%) were detected in many children with BHS but they were not significantly more in comparison to the controls.

Mean haemoglobin in the study group was 8.12 g/dL as compared to 9.92 g/dL in

the control group. The difference was statistically significant ($p<0.01$). Mean serum iron levels and percentage saturation of transferring were significantly lower in the study group compared to those in the control group. In 96% of cases in the study group, peripheral smear showed either hypochromic microcytic or hypochromic normocytic anemia. 82% cases responded to oral therapy within two weeks. After three weeks of therapy, all the cases showed improvement (either decrease in the severity or frequency of spells).

DiMario F. J. Jr (2000) in a prospective cohort study of 95 children with cyanotic and pallid BHS, documented the natural history of spells[31]. A structured interview was undertaken at the time of initial consultation and at subsequent one year intervals regarding the type of BHS, frequency of spells, associated phenomena, sequelae, family history, and age at termination of spells. Of 95 children, 48 were boys and 47 were girls. All children were followed over a 9 year interval. Median age of onset was between 6 and 12 months with 15% presenting younger than 6 months. A median frequency of spells was weekly with 30% experiencing 10 or more spells per day. The median age at peak frequency was between 12 and 18 months of age. Of the patients who remitted for >12 months (n=67), the last spell had occurred at a median age of 37 to 42 months. Hypoxic convulsions were associated with BHS in < 15% of all participants. A positive family history of BHS was identified in 34%, with equal distribution between both paternal and maternal sides.

Mocan H. et al., (1999) evaluated the prognosis of BHS after iron treatment in 91

children aged between 6 months and 40 months[24]. All cases were followed prospectively for a median of 45 months. In 49 children, the frequency of BHS was less than 10 each month, in 22 it was 10 – 30 each month and in 20 it was more than 30 each month. The spell was cyanotic in 60 children, pallid in 9 and mixed type in 22 children. All patients were evaluated initially and during follow up for haematological indices. 63 patients were found to be have iron deficiency anemia and were treated with iron (6mg/kg/day) for three months. Other patients were not given any treatment. After the three months, there was a significant difference for correction of cyanotic spells between children who were treated with iron and those who were not (84.17 vs 21.4 %). Positive family history of BHS was found in 9 (10%) of patients[24].

Donma M. M. et al., (1998) evaluated the efficacy of piracetam in the treatment of 76 children with breath holding spells[23]. It was a randomised blind placebo–controlled study. Piracetam was given in a dose of 40 mg/kg/day in two divided doses daily for two months. Children were evaluated after two months, and then at three- month intervals. After 2 months, the number of breath holding episodes per month decreased significantly in the piracetam-treated group. 92.3% of piracetam-treated children remained symptom-free during the next six months after completion of treatment. No major side effect was observed. The author concluded that piracetam is a safe and effective treatment option for the patients of BHS.

A study was done by Azam et al., to assess the role of piracetam in severe breath holding spells. Fifty-two children were enrolled in the study, 34 boys and 18 girls. Ages

ranged from 4 weeks to 5 years with mean age of 17 months. In 81% of children, spells disappeared completely and in 9% frequency was reduced to less than one per month and of much lesser intensity. Prophylaxis was given for 3-6 months (mean 5) duration. The authors concluded that piracetam was an effective prophylactic treatment for severe BHS[30].

STUDY JUSTIFICATION

Breath holding spells are often benign, but fairly common disorders affecting children. Various underlying autonomic nervous system abnormalities and brain stem dysfunction have been implicated recently in the pathogenesis of these spells. Rarely, life-threatening events such as status epilepticus and prolonged bradycardia or asystole may occur. But till date, research into available drug therapy has remained inadequate. Various drugs such as diazepam, sodium valproate, carbamazepine and phenobarbitone have been used based on sporadic reports of usefulness or for their anticonvulsant effect. Iron therapy has been found to reduce the frequency of spells in anaemic children with BHS. Piracetam is a new drug on the horizon. Few studies have been conducted in India. This study has been undertaken to study the clinical profile of BHS in the children attending our outpatient department, and to assess the role of diazepam and piracetam in the management of BHS. This study has been undertaken after obtaining the approval of the institutional review board in our hospital.

AIM OF THE STUDY

1. To study the clinical profile of children with breath holding spells

2. To study the role of diazepam and piracetam in the management of breath holding spells

SUBJECTS AND METHODS

STUDY DESIGN : Randomized controlled trial

STUDY POPULATION: Children attending the Neurology OP or the Child Guidance Clinic at ICH & HC, Chennai, and diagnosed as breath holding spell by history.

STUDY PERIOD : November 2006 to October 2008

SAMPLE SPECIFICATION :

Inclusion criteria

Children aged 1month to 5 years with history suggestive of breath holding spell as follows:-

Antecedent provocative event (anger/frustration/pain/fear) crying, progressively increasing in intensity → point of noiselessness → colour change (cyanosis/pallor) → resolution of features or loss of consciousness with or without seizure-like activity followed by resolution.

Exclusion criteria

Underlying cardiac disease
Underlying CNS pathology
Primary lung pathology

Sample size

Assuming an improvement of atleast 40% in the study groups as compared to the control group, and the power of the study to be 85%, sample size was calculated to be 30 per group, with a total of 90 cases.

PROPOSED METHODOLOGY:

90 children diagnosed to have breath holding spells by history and satisfying the study criteria were included in the study after obtaining written parental consent. A structured interview was conducted at the time of enrolment into the study (Proforma included in the Annexure). A complete physical examination was done and cardiac, neurological and respiratory diseases excluded clinically. EEG was taken to rule out true seizures. If the EEG was abnormal, the child was excluded from the study.

The children were then randomly allotted into one of the three groups- A, B or C using computer-generated random numbers. A baseline haemoglobin estimation was done to look for the presence of anemia in all children. Parental counselling was done regarding BHS, its treatment and prognosis. They were also given a patient information form containing information about breath holding spells. They were also advised to

maintain a spell diary everyday for information regarding number of spells per day.

Children allocated to Group A were given oral Diazepam 0.1 mg/kg/day in one or two divided doses.

Children in Group B were given oral Piracetam in a dose of 40 mg/kg/day in two divided doses.

Children in Group C did not receive either of these drug and were considered as the control group.

Children in all the three group with haemoglobin less than 11 mg/dL were also given oral iron in the form of ferrous sulphate at a dose of 6 mg/kg/day of elemental iron.

The total duration of theray was three months. During this period, children were reviewed every two weeks. The spell diary was seen to record the number of spells, and certain review questions asked (Follow up Questionnaire in Annexure). Drugs were issued once in two weeks at the time of review.

After completion of therapy, the children were followed up for one year, initially monthly visits for three months and then 3-monthly visits till the end of one year. A minimum of 3 visits was required to document adequate follow up; those with fewer visits were considered to be lost to follow up. Children with 50% or more reduction in the frequency of spells at completion of treatment were considered as cured. At completion of therapy, haemoglobin estimation was repeated to look for improvement in the haemoglobin status in these children.

If the child developed adverse reactions to the drug under study, or had a >50% increase in frequency of spells than at the time of enrolment into the study, he/she would be withdrawn from the study.

STATISTICAL METHODS FOR ANALYSIS OF RESULTS

All statistics were analysed using SPSS10 and EPI INFO software. Comparison of baseline characteristics was done using Chi Square Test. Pre – and Post treatment data were analysed using one-way ANOVA. Paired groups of data were analysed using Paired ‘t’ test. More than one group was analysed using ANOVA.

OBSERVATIONS

Total number of children with breath holding spells initially screened was 98. Out of this, 8 children (8.16%) were found to have abnormal EEG and hence were excluded from the study.

90 children were enrolled in the study after obtaining written parental consent. An information brochure regarding BHS was also handed over to the parents.

Table 1: AGE AT ONSET

AGE (IN MONTHS)	GROUP A N (%)	GROUP B N(%)	GROUP C N(%)	OVERALL N(%)
≤ 12	18 (60.0%)	15 (50.0%)	12 (40.0%)	45 (50.0%)
13 – 24	8 (26.7%)	11(36.7%)	9 (30.0%)	28 (31.1%)
25 –36	4 (13.3%)	4 (13.3%)	8 (26.7%)	16 (17.8%)
37 – 48	0 (0%)	0 (0%)	1 (3.3%)	1 (1.1%)
TOTAL	30	30	30	90

Out of the 90 children studied, 50% had onset of breath holding spells before one year of age, with 7 out of 90 children (7.7%) having onset before 6 months of age (Table 1).

Table 2: SEX DISTRIBUTION

SEX	GROUP A N (%)	GROUP B N(%)	GROUP C N(%)	OVERALL N(%)
MALE	20 (66.7%)	20 (66.7%)	15 (50%)	55 (61.1%)
FEMALE	10 (33.3%)	10 (33.3%)	15 (50%)	35 (38.9%)
TOTAL	30	30	30	90

The overall male: female ratio was found to be 1.6:1, indicating a slight male preponderance (Table 2).

Table 3: SPELL TYPE

SPELL TYPE	GROUP A N (%)	GROUP B N(%)	GROUP C N(%)	OVERALL N(%)
CYANOTIC	21 (70%)	20 (66.7%)	21 (70%)	62 (68.9%)
PALLID	5 (16.7%)	7 (23.3%)	7 (23.3%)	19 (21.1%)
MIXED	4 (13.3%)	3 (10.0%)	2 (6.7%)	9 (10.0%)
TOTAL	30	30	30	90

Cyanotic breath holding spells were seen in 68.9% of children and is the most common type of BHS. Pallid spells were seen in 21.1% of children, while both types of spells were seen in 10.0% of children (Table 3) .

Table 4: FREQUENCY OF SPELLS

NO.OF SPELLS PER WEEK	GROUP A	GROUP B	GROUP C	OVERALL
< 1	15 (50.0%)	13 (43.3%)	15 (50.0%)	43 (47.8%)
1 -3	9 (30.0%)	14 (46.7%)	8 (26.7%)	31 (34.4%)
4 -6	2 (6.7%)	1 (3.3%)	4 (13.3%)	7 (7.8%)
7 -10	2 (6.7%)	1(3.3%)	0 (0.0%)	3 (3.3%)
>10	2 (6.7%)	1 (3.3%)	3 10.0%)	6 (6.7%)
TOTAL	30	30	30	90

Maximum number of children (47.8%) had less than one episode per week. 34.4% of the children had between 1 to 3 episodes per week. About 6.7% of children had more than 10 episodes per week (Table 4).

Table 5: SEVERITY OF SPELLS

SEVERITY OF SPELL	GROUP A N (%)	GROUP B N (%)	GROUP C N (%)	OVERALL N (%)
SIMPLE	26 (86.7%)	23 (76.7%)	26 (86.7%)	75 (83.3%)
SEVERE	4 (13.3%)	7 (23.3%)	4 (13.3%)	15 (16.7%)
LIFE-THREATENING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOTAL	30	30	30	90

83.3% of children had simple breath holding spells without seizure activity. 16.7% of children developed hypoxic seizures at the end of the episode. None of the children in the study had life-threatening events such as status epilepticus or cardiac arrest requiring emergency medical intervention (Table 5).

Table 6: PRECIPITATING FACTORS

FACTOR	GROUP A N (%)	GROUP B N (%)	GROUP C N (%)	OVERALL N (%)
ANGER	16 (53.3%)	17 (56.7%)	19 (63.3%)	52 (57.8%)
PAIN	16 (53.3%)	18 (60.0%)	17 (56.7%)	51 (56.7%)
FEAR	7 (23.3%)	15 (50.0%)	5 (16.7%)	27 (30.0%)
>1 FACTOR	9 (30.0%)	17 (56.7%)	10 (33.3%)	36 (40%)

Anger (57.8%) was the most common factor precipitating the occurrence of breath holding spells, followed by pain (56.7%). Fear was the cause in 30% of children. More than one factor was implicated in 40% of children (Table 6).

Table 7: ASSOCIATED BEHAVIOURAL DISTURBANCES

	GROUP A N (%)	GROUP B N (%)	GROUP C N (%)	OVERALL N (%)
PICA	6 (20%)	6 (20%)	11 (36.7%)	23 (25.6%)
THUMB-SUCKING	7 (23.3%)	11 (36.7%)	10 (33.3%)	28 (31.1%)
NAIL-BITING	1 (3.3%)	0 (0.0%)	2 (6.7%)	3 (3.3%)
HEAD BANGING	9 (30%)	14 (46.7%)	8 (26.7%)	31 (34.4%)
INCESSANT CRY	5 (16.7%)	4 (13.3%)	5 (16.7%)	14 (15.6%)
TEMPER TANTRUMS	10 (33.3%)	12 (40.0%)	12 (40%)	34 (37.8%)
>1 FACTOR	11 (36.7%)	15 (50.0%)	13 (43.3%)	39 (43.3%)

Behaviour disturbances were noted in 73 out of 90 children (81%). The most common behaviour disturbance in these children was temper tantrums (37.8%), followed by head banging (34.4%). Thumb sucking was noted in 31.1%, pica in 25.6%, incessant cry in 15.6% and nail biting in 3.3% of the children. More than one behaviour disturbance was noted in 43.3% of the children (Table 7).

Table 8: TYPE OF FAMILY

TYPE OF FAMILY	GROUP A N (%)	GROUP B N (%)	GROUP C N (%)	OVERALL N (%)
JOINT	8 (26.7%)	11 (36.7%)	14 (46.7%)	33 (36.7%)
NUCLEAR	22 (73.3%)	19 (63.3%)	16 (53.3%)	57 (63.3%)
TOTAL	30	30	30	90

63.3% of children with breath holding spells came from a nuclear family, while 36.7% lived in a joint family (Table 8).

Table 9: FAMILY HISTORY

	GROUP A	GROUP B	GROUP C	OVERALL
BREATH-HOLDING SPELL	1	0	5	6
SEIZURE	1	0	3	4

A positive family history of breath holding spells was present in 6 out of 90 children (6.7%). 4 out of 90 children also had a positive family history of seizures (4.4%) (Table 9).

Table 10: PRESENCE OF CLINICAL PALLOR AND ANEMIA

	GROUP A N (%)	GROUP B N (%)	GROUP C N (%)	OVERALL N (%)
PALLOR	8 (26.7%)	9 (30.0%)	10 (33.3%)	27 (30.0%)
ANEMIA	24 (80.0%)	20 (66.7%)	21 (70.0%)	65 (72.2%)
NO ANEMIA	6 (20.0%)	10 (33.3%)	9 (30.0%)	25 (27.8%)
TOTAL	30	30	30	90

Clinically, pallor could be made out in 30% of the children, whereas 72.2% of the children had anemia as evidenced by hemoglobin less than 11g/dL. 27.8% of the children had haemoglobin 11g/dL or more (Table 10).

The frequency of breath holding spells was assessed at the time of enrolment into the study, at the completion of three-month treatment period, and during follow up for two years. One child in Group B was lost to followup.

Table 11: COMPARISON OF REDUCTION IN FREQUENCY OF SPELLS AT COMPLETION OF TREATMENT AND AT FOLLOW-UP AMONG THE THREE GROUPS

	GROUP						Oneway ANOVA F-test	REPEATED MEASURES OF ANOVA
	A		B		C			
	Mean	SD	Mean	SD	Mean	SD		
FREQ of spells pre-treatment	3.29	3.96	3.17	4.60	3.83	6.10	F=0.15 P=0.86	**Within group F=48.33 P=0.001**
FREQ of spells at completion of treatment	1.80	2.66	1.86	3.65	2.27	3.53	F=0.18 P=0.84	
FREQ of spells at 3 months follow up	.53	1.14	.41	1.35	.57	1.52	F=0.11 P=0.90	
FREQ of spells at 1 yr follow up	.13	.43	.07	.37	.13	.57	F=0.19 P=0.83	Between group F=0.13 P=0.88
One way ANOVA	F=48.71 P=0.001		F=6.68 P=0.001		F=6.60 P=0.001			

Prior to treatment, the mean frequency of spells per week in Group A was 3.29. The mean frequency of spells in Group B was 3.17. The mean frequency of spells in Group C was 3.83. The three groups were comparable with respect to baseline characteristics (Table 11).

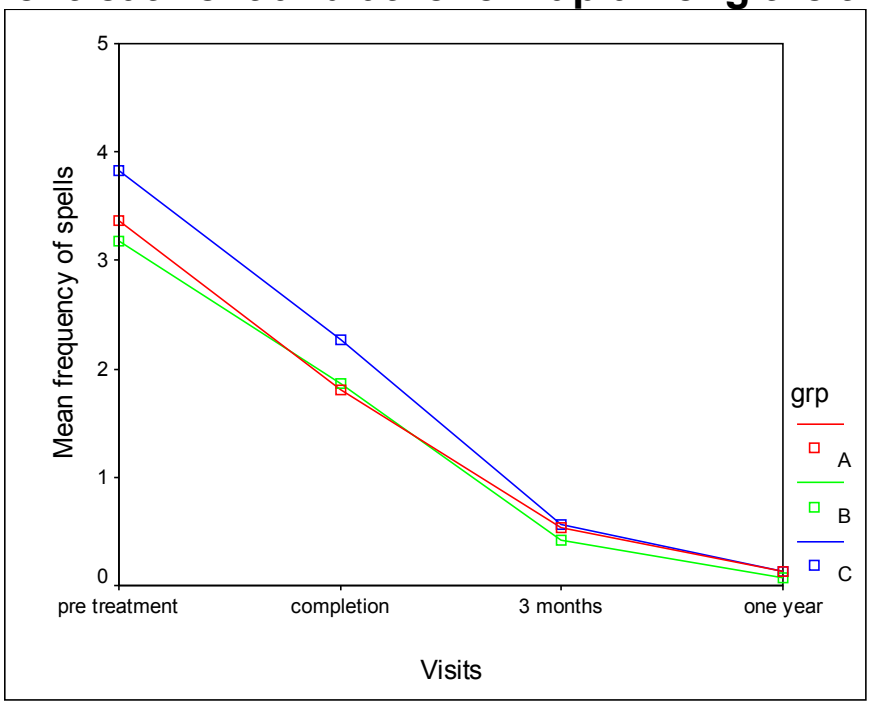
On completion of treatment, the mean frequency was 1.80 spells per week in Group A, 1.86 in Group B and 2.27 in Group C. The mean frequency of spells was lower in Groups A and B, but this difference was not statistically significant.

Following treatment for three months, the mean frequency of spells decreased by

45% in Group A, 41% in Group B and 41% in Group C. Though the reduction was more in the Diazepam group, it was not found to be statistically significant (p =0.88).

At the end of one year of follow up, the mean frequency of spells per week was 0.13 in Group A, 0.07 in Group B and 0.13 in Group C. The difference between the groups was not statistically significant.

(Fig. 10) Comparison of reduction in frequency of spells at completion of treatment and at follow-up among the three groups



The number of children who could be considered cured as evidenced by reduction in spell frequency by atleast 50% at the end of treatment was 76.7% in Group A, 93.3% in Group B and 90% in Group C. The difference was not statistically significant (P=0.55) (Fig. 10).

Table 12: COMPARISON OF MAXIMUM SPELL-FREE PERIOD BETWEEN

THE THREE GROUPS

	N	Mean	Std. Deviation	One way ANOVA F-test
A	30	8.70	4.178	
B	29	10.31	3.516	F=1.79 P=0.17
C	30	10.33	3.745	
Total	**89**	**9.78**	**3.861**	

The mean maximum spell-free interval was found to be 8.70 months in Group A, 10.31 months in Group B and 10.33 months in Group B. This was analysed by one- way ANOVA and it was found that there was no statistically significant difference between the three groups (Table 12).

During treatment period no adverse drug reactions or problems were complained of. During follow up, one child in Group C was admitted for bronchopneumonia and was discharged after 7 days following clinical improvement.

Table 13: COMPARISON OF PRE- & POST- TREATMENT HEMOGLOBIN CONCENTRATION AMONG THE THREE GROUPS

Group		Mean	Std. Deviation	Student paired t-test

A	**Pre-Treatment HB**	10.01	1.124	t=15.68 P=0.001
	Post-Treatment HB	11.65	.761	
B	Pre-Treatment HB	10.11	1.361	t=16.36 P=0.001
	Post-Treatment HB	11.72	1.097	
C	Pre-Treatment HB	10.22	1.164	t=16.82 P=0.001
	Post-Treatment HB	11.83	.810	

The mean pre-treatment haemoglobin in Group A was 10.1g/dL, in Group B was 10.11g/dL and in Group C was 10.22g/dL. After the completion of treatment, haemoglobin levels were reassessed. The mean haemoglobin in Group A was 11.65g/dL, in Group B was 11.72g/dL and in Group C was 11.83g/dL. There was no statistically significant difference between the three groups (p=0.86) (Table 13).

Table 14: COMPARISON OF MEAN RISE IN HEMOGLOBIN CONCENTRATION AMONG THE 3 GROUPS

	N	Mean	Std. Deviation	One way ANOVA F-test
A	30	1.60	.548	F=0.02 P=0.99
B	29	1.61	.530	
C	30	1.61	.524	
Total	89	1.61	.528	

The mean rise in haemoglobin was 1.60g/dL, 1.61g/dL and 1.61g/dL in Group A, Group B and Group C respectively. The difference between the three groups was not statistically significant (Table 14).

DISCUSSION

In our study, out of 90 children with breath holding spells studied, the median age of onset was 12.46 months (range 4 months to 4 years). In the studies by Bhatia M. S, et al.,[23] Mocan H et al.,[24] and Anil B. G et al.[15] the mean age of onset was 9.6 months, 17 months and 14.2 months respectively. In our study, 45 children (50%) had onset of BHS before one year of age, with 7 children (7.7%) experiencing their first spell before six months of age. Bridge et al.[1] and Lombroso and Lerman[2] had reported the age of onset from the neonatal period to about four years.

In our study, out of 90 children, there was a male preponderance with a male: female ratio of 1.6:1. This is similar to earlier studies by Bhatia M. S. et al.[19] (M:F=3:1), Mocan H et al.[20] (M:F=1.6:1) and Anil B. G. et al.[15] (3:2). But DiMario has reported equal incidence of BHS in both sexes in his study.

68.9% of children in our study had cyanotic type of BHS, 21.1% had pallid type while 10.0% had mixed type of spells. In the study by Bhatia M. S. et al.[19], 96% had cyanotic type while 4% had pallid type of BHS.

Lombroso and Lerman[2], Livingston[1], Bhatia M. S. et al.[19] and Anil B. G. et al have reported tonic-clonic convulsions in 46%, 49%, 84% and 82% respectively. In our study, convulsions were observed in 16.7% of the children. None of them had life-threatening events like status epilepticus or cardiac arrest.

47.8% of the children in our study had less than 1 spell per week, followed by 34.4% of children with 1-3 spells per week. 6.7% of children had more than 10 spells per week. In the study by Anil B. G. et al.[15], they have reported 58% of children had frequency of spells as 1-3 per week. Bhatia M. S. et al.[19] also have reported in their study that majority of the children had frequency of spell as 1-3 per week.

In our study, anger was the triggering factor in the majority of children (57.8%), followed by fear (56.7%). Pain was the triggering factor in 30% of the children. More than one factor was implicated in 40% of the children in our study. In the study by Anil B. G. et al.[15], anger or frustration were the triggering factors in 82% of children followed by fall (14%), and fear or pain (4%).

As reported by Bakwin and Bakwin[5], Bhatia M. S. et al.[19] and Anil B. G. et al.[15], several behaviour problems have been reported in our children also. The most common behaviour disturbance in these children was temper tantrums (37.8%), followed by head banging (34.4%). More than one problem was present in 43.3% of the children in our study.

63.3% of children with breath holding spells came from a nuclear family, while 36.7% lived in a joint family.

A positive family history of breath holding spells was present in 6 out of 90 children (6.7%). 4 out of 90 children also had a positive family history of seizures

(4.4%). In the study by DiMario F. J. Jr.[16], 21% of the siblings and 27% of parents reported either current or past history of BHS.

Clinically, pallor could be made out in 30% of the children, whereas 72.2% of the children had anemia as evidenced by hemoglobin less than 11g/dL. 27.8% of the children had haemoglobin 11g/dL or more.

Prior to treatment, the mean frequency of spells per week in Group A was 3.29. The mean frequency of spells in Group B was 3.17. The mean frequency of spells in Group C was 3.83. The three groups were comparable with respect to baseline characteristics (p value>0.5).

The three Groups were again compared following completion of treatment. None of the children were withdrawn from the study on account of adverse reaction to the drugs used. One child in Group B was lost to follow up.

On completion of treatment, the mean frequency was 1.80 spells per week in Group A, 1.86 in Group B and 2.27 in Group C. The mean frequency of spells was lower in Groups A and B, but this difference was not statistically significant.

Following treatment for three months, the mean frequency of spells decreased by 45% in Group A, 41% in Group B and 41% in Group C. Though the reduction was more in the Diazepam group, it was not found to be statistically significant (p= 0.88).

At the end of one year of follow up, the mean frequency of spells per week was 0.13 in Group A, 0.07 in Group B and 0.13 in Group C. The difference between the groups was not statistically significant.

The number of children who could be considered cured as evidenced by reduction in spell frequency by atleast 50% at the end of treatment was 23 (76.7%) in Group A, 28 (93.3%) in Group B and 27(90%) in Group C. Though more children appeared to be cured in Group A as compared to the other two groups, the difference was not statistically significant ($p= 0.55$).

The mean maximum spell-free interval was found to be 8.70 months in Group A, 10.31 months in Group B and 10.33 months in Group B. This was analysed by one- way ANOVA and it was found that there was no statistically significant difference between the three groups.

In the study conducted by Donma[23], placebo or piracetam as suspension was administered to patients on a randomized basis; piracetam was administered to children in suspension 40 mg/kg/day in 2 divided doses for a period of 2 months. Of the 76 children enrolled, 39 received piracetam and 37 received placebo. Overall, control of breath-holding spells was observed in 92.3% of the patients in the group taking piracetam as compared with 29.7% in the group taking placebo ($p<0.5$).

A similar study was done by Azam M et al.[30]. Fifty-two children were enrolled in

the study, 34 boys and 18 girls. Ages ranged from 4 weeks to 5 years with mean age of 17 months. Prophylaxis was given for 3 to 6 months Piracetam was prescribed to those children who were diagnosed as severe BHS in a dose ranging from 50-100 mg/kg/day, which is a higher dose than that used in our study. Iron supplements were added if hemoglobin was less than 10 gm%. Patients were seen at 2-4 weeks interval and follow-up was continued until 3 months after the cessation of drug therapy. In 81% of children, spells disappeared completely and in 9% frequency was reduced to less than one per month and of much lesser intensity.

There is no comparable trial previously done for the role of diazepam. In our study, iron was also prescribed to children who were anemic, since there are several trials documenting the efficacy of iron in reducing the frequency of breath holding spells. The use of iron in anemic breath holders in all 3 groups has probably led to comparable reduction in spell frequency and cure rates among all 3 groups.

SUMMARY AND CONCLUSION

- Half the children had onset of spells before one year of age.
- There was a male preponderance in the occurrence of spells noted in our study.
- 68% of spells were cyanotic type.
- Tonic-clonic movements were present in 16% of children with BHS in our study.
- 47% of children had frequency of spells less than one per week and 6.7% of children had more than 10 spells per week.
- Anger and pain were the most common triggering factors in 57.8% and 56.7% of children, respectively.
- Behaviour abnormalities were reported in 81% of the children, with temper tantrums being the most common (37.8%).
- A positive family history of BHS was present in 6.7% of the children only.
- There was a significant reduction in the frequency of spells in each group following treatment, but the there was no statistically significant difference between the groups.
- The cure rate following treatment was also comparable among the three groups.

- Neither diazepam nor piracetam was found to produce a statistically significant maximum spell-free interval more than the control group.

- The mean haemoglobin levels, pre- and post- treatment were comparable in all three groups.

From this study, we conclude that the role of diazepam and piracetam was not found to be significant as compared to the control group, though there are reports to the contrary. The role of diazepam or piracetam in the sub group of children with severe breath holding spells has to be studied. Further studies with a larger study population or in children with severe breath holding spells would be required before we can arrive at a definite conclusion.

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PATIENT INFORMATION FORM

What are breath-holding spells?

Breath-holding spells are considered to be a behavioural disorder in children. This is fairly common, occurring in upto 27% of otherwise healthy children, and may be severe in about 0.1 – 4.6% of children. This commonly occurs in children between six months to five years and has been found to subside on its own as the child grows.

How to recognise a spell?

When a child is provoked as being refused chocolates or scolded for a mischief, or following painful stimulation such as injections, he/ she starts crying. This increases to a point of noiselessness, where the child's breathing stops in expiration. He turns blue or pale, and becomes limp.the child may lose consciousness, and develop jerking of limbs similar to a seizure. After a few minutes, he regains consciousness.

What should be done during a spell?

The child must be placed in a lying posture in a safe place. If there is jerking of limbs, the child must be turned to one side, and adjacent sharp objects removed, so that he does not get hurt. If the child is not breathing or does not recover in five minutes, medical help must be sought.

What must not be done?

When the child develops a spell, he must not be picked up and fondled. Any unfair demands must not be fulfilled in order to prevent a spell. If done so, this behaviour is reinforced, and becomes difficult to control.

Is there any treatment for breath-holding spells?

Behaviour modification forms the basis of treatment. It is important for the parents to avoid fondling or hugging the child following a spell. Iron supplementation has been found to be useful in anemic children. Certain drugs have been found useful in control of spells, primarily by their effect in calming the child. If the spells are severe, with continuing seizures, or prolonged unresponsiveness, immediate medical attention is essential.

ROLE OF DIAZEPAM AND PIRACETAM IN THE MANAGEMENT OF BREATH-HOLDING SPELLS

PATIENT DATA ENTRY FORM

PATIENT DETAILS :

Name
Age / Sex
Address and contact number
Informant
CGC No / Neurology No
STUDY NO AND GROUP -

HISTORY :

Age at onset
Type of spell –

1. Cyanotic
2. Pallid
3. Mixed

Frequency per week –

c. <1
d. 1-3
e. 4-6
f. 7-10
g. >10

Severity of spell –

1. Simple
2. Severe
3. Life – threatening

Precipitating factors –

1. Anger
2. Pain
3. Fear

Associated behaviour disturbance –

g. Pica
h. Thumb-sucking
i. Nail biting
j. Head-banging
k. Incessant cry
l. Temper tantrums
m. Other (specify)

Maternal history –

1. Maternal illness
2. Drug intake
3. Others (specify)

Perinatal history –

1. Birth asphyxia
2. Neonatal seizures
3. Others (specify)

Developmental milestones –

1. Normal
2. Delayed

Type of family –

1. Joint
2. Nuclear

Family history of BHS –

1. Yes
2. No

Family history of seizures –

1. Yes
2. No

CLINICAL ASSESSMENT :

Physical examination –

Pallor –

1. Yes
2. No

System examination –

1. Normal
2. Abnormal

If any abnormality detected, please specify

Haemoglobin -

1. ≥11g/dL
2. <11 g/dL

EEG –

1. Normal
2. Abnormal

Additional details, if any

FOLLOW UP QUESTIONNAIRE

During therapy –

1. Did the child have any BHS since the last visit? Yes/ no
2. How many episodes per week ? <1 /1-3/ 4-6/ 7-10/ >10
3. Severity of the episode – simple/ severe/ life threatening
4. Other significant problem or illness since the last visit? Yes / no
5. Whether drug compliance was good? Yes/ no
6. Any adverse drug reactions? Yes / no, if yes, specify

After completion of therapy-

1. Did the child have any BHS since the last visit? Yes/ no
2. How many episodes per week? <1/ 1-3/ 4-6/ 7-10/ >10
3. How severe was the episode – simple/ severe / life threatening

Investigations-

- Haemoglobin level on completion of therapy : <11 g/dL , ≥ 11g/dL